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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

HM12/0617

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ART UNIT	PAPER NUMBER
SWARTZ R 1641	11

DATE MAILED: 06/17/99

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 4-5-99 & 4-22-99

☒ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire — 3 — month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 28-40, 42-55 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 28-40, 42-55 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 10
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. Applicants' Response to Office Action, received 5April1999, paper#9, is acknowledged. Claims 1-27 and 41 have been canceled without prejudice. Claims 28 and 40 have been amended. New claims 42-55 have been added.

2. Currently, claim 28-40 and 42-55 are under consideration.

Information Disclosure Statement

3. Reference 73 on applicants' Form PTO-1449, has not been considered because of the uncertainty of **when or even if** the material was made public or presented. The reference appears to be a hard copy of a slide which, according to the PTO-1449, "may have been (but was probably not) presented at a seminar" by the author.

Rejections Withdrawn

4. The rejection of claims 28-40 under 35 U.S.C. 112, second paragraph, as being dependent to a nonelected claim is withdrawn in light of the amendment of claims 28 and 40.

5. The rejection of claims 30-31 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Lewis et al (*Cancer Immunol. Immunother.*, 37:255-263, 1993) is withdrawn.

Rejections Maintained

6. The rejection of claims 28-31, 37-38 and 40 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Shepard et al (*J. Clin. Immunol.*, 11(3):117-127, 1991) is maintained.

The claims are drawn to a method for inducing cell death comprising exposing a cell which over expresses ErbB2 to an effective amount of an antibody which binds to Domain 1 of ErbB2..

Applicants argue that the cited references fail to anticipate the invention for several reasons.

Applicants argue that the cited references concerning 4D5 antibody or humanized 4D5 do not anticipate the invention in claim 28 because the 4D5 antibody in the cited references do not bind Domain 1 at the amino terminus of the extracellular domain of ErbB2.

Applicants argue that the cited references do not disclose that monoclonal antibodies 7C2 and 7F3 bind Domain 1 of ErbB2, nor provide sufficient structural information such that the skilled person could have reproduced those particular antibodies. Therefore, the cited references fail to teach a method for inducing cell death using an antibody which binds to Domain 1 of ErbB2.

Applicants argue that in relation to claim 40, the 4D5 antibody in the cited references and humanized 4D5 in Lewis et al do not result in about 5-50 fold induction of annexin binding relative to untreated cell in an annexin binding assay using BT474 cells, thus failing to anticipate the invention set forth in claim 40.

Applicants argue that concerning the 7C2 and 7F3 antibodies, the cited references do not disclose that these antibodies result in about 5-50 fold induction of annexin binding relative to untreated cell in an annexin binding assay using BT474 cells, nor do the references make available to the skilled person these antibodies.

Applicants argue that the claimed invention would not have been obvious over the cited references for several reasons.

Applicants argue that there is no suggestion in the cited references that Domain 1 is a useful region of ErbB2 for targeting with antibodies, much less that such antibodies can be used to induce death of a cell, such as a cancer cell, which over expresses ErbB2.

Applicants argue that the cited references do not disclose a method of treating a mammal with the claimed antibody which binds to Domain 1 of ErbB2.

Applicants argue that there is nothing in the cited references suggesting that an antibody which binds to ErbB2 and results in about 5-50 fold induction of annexin binding relative to untreated cell in an annexin binding assay using BT474 cells, much less that such an antibody would be useful in the claimed method.

The examiner has considered applicants' arguments, but does not find them persuasive because, in the absence of evidence to the contrary, antibodies 7C2, 7F3, and 4D5 in the instant application are the same antibodies in the cited references because applicant Brian M. Fendly, of Genentech, Inc., is also the co-author on both cited references, which also list Genentech, Inc. as the address of correspondence. Both the instant application and the cited references also teach that the antibodies bind to ErbB2. Therefore, the antibodies are the same because: 1) same laboratory, 2) same author/applicant, 3) same laboratory designation for the antibodies, 4) same procedures for producing antibodies, and 5) same reactivity, i.e., bind to ErbB2(HER2).

Since the **same laboratory designation** is utilized in both the instant application and the cited references, **from the same laboratory**, the properties of antibodies 7C2, 7F3 and 4D5 in the cited references are inherent concerning: 1) binding to Domain 1 of ErbB2, 2) binding another Domain, and 3) 5-50 fold induction of annexin binding.

Shepard et al teach a monocional anti-HER2 antibody (4D5) which: a) inhibits the growth of SKBR3 breast tumor cells in cell culture by 66% (Abstract; Table II); b) enhances the sensitivity of SKBR3 cells to cisplatin (Figure 5); and c) enhances the sensitivity of SKBR3 cells to TNFα (Figure 4). Shepard et al also teach monoclonal anti-HER2 antibodies 7C2 and 7F3 which bind to Domain 1 of ErbB2 (Figure 2; page 119, section **Derivation of muMab 4D5**) and which inhibit SKBR3 proliferation by 21% and 38% respectively (Table II).

Shepard et al teach a **nude mouse model** wherein the antibody localizes at the tumor site and **inhibits growth of human** tumor xenografts which over express HER2(ErbB2) (section ***In vivo* Preclinical Efficacy**, page 122-123). Shepard et al suggest, that based upon such *in vivo* data, over expression of the protein in human cancer makes this receptor an attractive target for development of cancer therapeutics (page 126, lines 5-8).

7. The rejection of claims 28-29, 37-38 and 40 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Lewis et al (*Cancer Immunol. Immunother.*, 37:255-263, 1993) is maintained.

Applicants argue that the cited references fail to anticipate the invention for several reasons.

Applicants argue that the cited references concerning 4D5 antibody or humanized 4D5 do not anticipate the invention in claim 28 because the 4D5 antibody in the cited references do not bind Domain 1 at the amino terminus of the extracellular domain of ErbB2.

Applicants argue that the cited references do not disclose that monoclonal antibodies 7C2 and 7F3 bind Domain 1 of ErbB2, nor provide sufficient structural information such that the skilled person could have reproduced those particular antibodies. Therefore, the cited references fail to teach a method for inducing cell death using an antibody which binds to Domain 1 of ErbB2.

Applicants argue that in relation to claim 40, the 4D5 antibody in the cited references and humanized 4D5 in Lewis et al do not result in about 5-50 fold induction of annexin binding relative to untreated cell in an annexin binding assay using BT474 cells, thus failing to anticipate the invention set forth in claim 40.

Applicants argue that concerning the 7C2 and 7F3 antibodies, the cited references do not disclose that these antibodies result in about 5-50 fold induction of annexin binding relative to untreated cell in an annexin binding assay using BT474 cells, nor do the references make available to the skilled person these antibodies.

Applicants argue that the claimed invention would not have been obvious over the cited references for several reasons.

Applicants argue that there is no suggestion in the cited references that Domain 1 is a useful region of ErbB2 for targeting with antibodies, much less that such antibodies can be used to induce death of a cell, such as a cancer cell, which over expresses ErbB2.

Applicants argue that the cited references do not disclose a method of treating a mammal with the claimed antibody which binds to Domain 1 of ErbB2.

Applicants argue that there is nothing in the cited references suggesting that an antibody which binds to ErbB2 and results in about 5-50 fold induction of annexin binding relative to untreated cell in an annexin binding assay using BT474 cells, much less that such an antibody would be useful in the claimed method.

The examiner has considered applicants' arguments, but does not find them persuasive because, in the absence of evidence to the contrary, antibodies 7C2, 7F3, and 4D5 in the instant application are the same antibodies in the cited references because applicant Brian M. Fendly, of Genentech, Inc., is also the co-author on both cited references, which also list Genentech, Inc. as the address of correspondence. Both the instant application and the cited references also teach that the antibodies bind to ErbB2. Therefore, the antibodies are the same because: 1) same laboratory, 2) same author/applicant, 3) same laboratory designation for the antibodies, 4) same procedures for producing antibodies, and 5) same reactivity, i.e., bind to ErbB2(HER2).

Since the **same laboratory designation** is utilized in both the instant application and the cited references, **from the same laboratory**, the properties of antibodies 7C2, 7F3 and 4D5 in

the cited references are inherent concerning: 1) binding to Domain 1 of ErbB2, 2) binding another Domain, and 3) 5-50 fold induction of annexin binding.

Lewis et al teach monoclonal anti-HER2 monoclonal antibodies, e.g., 4D5, 7C2, and 7F3, which inhibit **human tumor** cells such as SKBR3 (Table 2) and mediate antibody-dependent cellular cytotoxicity (Figure 4).

8. The rejection of claims 32-36, and 39 under 35 U.S.C. 103(a) as being unpatentable Shepard et al (*J. Clin. Immunol.*, 11(3):117-127, 1991), or Lewis et al (*Cancer Immunol. Immunother.*, 37:255-263, 1993), in view of Fendly et al (*Cancer Research*, 50:1550-1558, 1990), Deshane et al (*J. Invest. Med.*, 43(Suppl 2):328A, 1995), and further in view of Senter et al (U.S. Pat. No. 4,975,278) is maintained.

Applicants argue that cited references Shepard et al, and Lewis et al, do not make available the specific 7C2 or 7F3 antibodies.

The examiner has considered applicants' argument, but does find it persuasive. See discussions above, sections **5** and **6**.

Applicants argue that Fendly et al is similarly deficient in failing to describe antibodies with properties (a) or (b), or to sufficiently describe the structural characteristics of the anti-ErbB2 antibodies designated 7C2 or 7F3 to enable those particular antibodies.

The examiner has considered applicants' argument, but does not find them persuasive because, in the absence of evidence to the contrary, antibodies 7C2, 7F3, and 4D5 in the instant application are the same antibodies in the cited references because applicant Brian M. Fendly, of

Genentech, Inc., is also the co-author on both cited references, which also list Genentech, Inc. as the address of correspondence. Both the instant application and the cited references also teach that the antibodies bind to ErbB2. Therefore, the antibodies are the same because: 1) same laboratory, 2) same author/applicant, 3) same laboratory designation for the antibodies, 4) same procedures for producing antibodies, and 5) same reactivity, i.e., bind to ErbB2(HER2).

Applicants argue that Deshane fails to teach an anti-ErbB2 antibody used in the methods claimed in the present application.

The examiner has considered applicants' argument, but does not find it persuasive. Deshane et al is cited as support of the other cited references to show that antibody knockout of the ErbB2 oncoprotein achieves targeted eradication of tumor targets by induction of apoptosis. Deshane et al is not cited as a reference for the specifically designated, 7C2, 7F3, or 4D5.

Applicants argue that Senter et al is silent concerning anti-ErbB2 antibodies and their properties, thus failing to supply the deficiencies of the other cited references.

The examiner has considered applicants' argument, but does not find it persuasive. Senter et al is cited to illustrate a delivery system of antibodies to tumors cells.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 42-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shepard et al (*J. Clin. Immunol.*, 11(3):117-127, 1991), in view of Lewis et al (*Cancer Immunol. Immunother.*, 37:255-263, 1993) and Fendly et al (*Cancer Research*, 50:1550-1558, 1990), and further in view of Deshane et al (*J. Invest. Med.*, 43(Suppl 2):328A, 1995) and Senter et al (U.S. Pat. No. 4,975,278).

The instant claims utilize the open language "comprising" in delineating the methods steps. Such language encompasses induction of apoptosis which is taught in the instant specification as one of the mechanisms by which the claimed antibodies induce cell death, but the scope of the claim is not restricted only to apoptosis, nor is the language restricted as to the use of other reagents, such as complement, phagocytic cells, cytotoxic drugs, or growth inhibitory agents, in addition to the antibodies.

In the absence of evidence to the contrary, antibodies 7C2, 7F3, and 4D5 in the instant application are the same antibodies in the cited references, Shepard et al, Lewis et al, and Fendly et al, because applicant Brian M. Fendly, of Genentech, Inc., is also the co-author on these cited references, which also list Genentech, Inc. as the address of correspondence. Both the instant application and the cited references also teach that the antibodies bind to ErbB2. Therefore, the antibodies are the same because: 1) same laboratory, 2) same author/applicant, 3) same laboratory

designation for the antibodies, 4) same procedures for producing antibodies, and 5) same reactivity, i.e., bind to ErbB2(HER2).

Lewis et al also teach monoclonal anti-HER2 monoclonal antibodies, e.g., 4D5, 7C2, and 7F3, which inhibit human tumor cells (Table 2) and mediate antibody-dependent cellular cytotoxicity (Figure 4). While Lewis et al do not teach that antibodies 7C2 and 7F3 bind to Domain 1 of ErbB2, the antibodies taught by Lewis et al would bind to Domain 1 of ErbB2, as these antibodies the same as those of the instant application, in the absence of evidence to the contrary (see discussion above). Lewis et al do not teach *in vivo* administration of the antibodies, but do suggest that these antibodies will add to the repertoire of therapeutic agents directed against human cancers characterized by amplification of the HER2 protooncogene (page 262, end of column 1). While Lewis et al do teach exposing a tumor cell to an antibody which does not bind to Domain 1 of ErbB2 (4D5), Lewis et al do not teach such exposure in conjunction with another antibody. Lewis et al do not teach that cell death is induced by apoptosis.

Shepard et al teach a monoclonal anti-HER2 antibody (4D5) which: a) inhibits the growth of SKBR3 breast tumor cells in cell culture by 66% (Abstract; Table II); b) enhances the sensitivity of SKBR3 cells to cisplatin (Figure 5); and c) enhances the sensitivity of SKBR3 cells to TNFα (Figure 4). Shepard et al also teach monoclonal anti-HER2 antibodies 7C2 and 7F3 which bind to Domain 1 of ErbB2 (Figure 2; page 119, section **Derivation of muMab 4D5**) and which inhibit SKBR3 proliferation by 21% and 38% respectively (Table II). Shepard et al teach a **nude mouse model** wherein the antibody localizes at the tumor site and **inhibits growth of**

human tumor xenografts which over express HER2(ErbB2) (section ***In vivo* Preclinical Efficacy**, page 122-123). Shepard et al suggest, that based upon such *in vivo* data, over expression of the protein in human cancer makes this receptor an attractive target for development of cancer therapeutics (page 126, lines 5-8). Shepard et al does not teach exposing a tumor cell to more than one antibody at a time. Shepard et al do not teach that cell death is induced by apoptosis.

Fendly et al is cited to teach the production and characterization of the monoclonal anti-HER2 antibodies utilized by Shepard et al and Lewis et al (Abstract; page 1550-1552, section **Materials and Methods**).

Deshane et al is cited to teach that intracellular antibody knockout of the ErbB2 oncoprotein (to which the antibodies 4D5, 7C2, and 7F3 bind) achieves targeted eradication of tumor targets by induction of apoptosis.

Senter et al is cited to teach methods of chemotherapeutic agent delivery to tumor cells by using tumor specific antibody/enzyme conjugates that bind to tumor cells. Upon additional administration of a prodrug, the enzyme converts the prodrug into an active chemotherapeutic agent (Abstract; Figure 1, column 4, line 5 to column 5, line 4).

Thus, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to use the monoclonal anti-HER2 monoclonal antibodies, such as 4D5, 7C2, and 7F3, as taught by Shepard et al, Lewis et al, and Fendly et al to induce cell death in cells over expressing ErbB2 receptor, either by utilizing the antibodies individually, or to maximize

efficacy, utilizing combinations of the antibodies. Likewise, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to enhance the efficacy of the monoclonal antibodies by using the chemotherapeutic agents and techniques taught by Senter et al, or by using in concert with the monoclonal antibody treatment, radiation treatments as widely used in the treatment of tumors.

Conclusion

11. No claims are allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rodney P. Swartz, Ph.D., whose telephone number is (703) 308-4244. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4:00 PM EST.

If attempts to reach the Examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703)308-4027. The facsimile telephone number for the Art Unit Group is (703)308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703)308-0196.

Rodney P Swartz PhD

RODNEY SWARTZ
PATENT EXAMINER

June 16, 1999

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